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EXAMINER

WILSON, MICHAEL C

ART UNIT

PAPER NUMBER

1632

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39

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/160,076

Applicant(s)

SCOTT ET AL.

Examiner

Michael Wilson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 June 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 69-78 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 69-78 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: *detailed action*.

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DETAILED ACTION

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1632.

Claims 52-68 have been canceled. Claims 69-78 have been added. Claims 69-78 are pending and under consideration in the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant's arguments filed 6-20-02, paper number 37, have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 112

The rejection of claims 65 and 66 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention has been withdrawn because the claims have been canceled.

1. Claim 75 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

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The term "transduction" in claim 75 is new matter. Page 42, line 8, teaches transfecting. Page 42, line 11, teaches infecting. The specification does not contemplate "transduction." It is not readily apparent that "transfecting" or "infecting" is "transduction." In fact, "transfecting," "infecting," and "transducing" may all be different processes.

2. Claims 69-78 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 69 is directed toward a composition for inducing tolerance to an antigen comprising a non-tumor lymphoid cell transfected with a vector encoding a fusion protein comprising i) an immunoglobulin heavy or light chain and ii) a protein having an epitope of the antigen to which tolerance is desired, wherein said composition induces tolerance to the antigen. The specification does not provide adequate written description for any fusion protein that induces tolerance in a host. Therefore, the specification does not provide adequate written description for any non-tumor lymphoid cell that induces tolerance in a host as claimed because the cell requires DNA encoding such a fusion protein.

The specification teaches transfecting non-tumor bone marrow cells with a retroviral vector encoding a fusion protein comprising amino acids 12-26 of bacteriophage lambda c1 protein and an IgG heavy chain (pg 42, Example 5). Zambidis (1997, Molecular Med., Vol. 3, pg 2174-82) taught administering the retrovirally transduced bone marrow cells to mice, injecting

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the mice later with 12-26 peptide or a control antigen, testing the antibody and CTL response of the mice, and comparing the response of test mice to controls wherein a decreased antibody or CTL response in the test mice as compared to controls indicated the cells induced tolerance against the bacteriophage lambda c1 protein (pg 213, col. 2, last 4 lines; pg 214, col. 2, "Tolerance..."). However, neither the specification or Zambidis provide a reason why one of skill would want to induce tolerance against the lambda c1 protein. Therefore, the 12-26 peptide is not an "antigen to which tolerance is desired" as claimed.

Assuming, to the contrary, that the bacteriophage lambda c1 12-26 peptide disclosed is an "antigen to which tolerance is desired," the specification does not teach any other proteins that induce tolerance, correlate the structure of the 12-26 peptide to any other protein, or correlate the results described in Zambidis to any other proteins. The specification suggests other possible proteins that may have antigens to which tolerance is desired, but the specification does not teach the antigens or epitopes within the antigens that are adequate to induce tolerance in a host. Nor did the art at the time of filing teach antigens that were able to induce tolerance in a host. In view of the lack of compositions as claimed that induce tolerance, taken with the one composition disclosed in the specification capable of inducing tolerance, the specification does not provide adequate written description for any and all cells that induce tolerance as broadly claimed. Disclosure of one fusion protein that induces tolerance (12-26 peptide-IgG) is not adequate written description for the host of embodiments encompassed by a fusion protein comprising "i)

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an immunoglobulin heavy or light chain and ii) a protein having an epitope of the antigen to which tolerance is desired” as claimed.

The specification does not provide adequate written description for any nucleic acid sequence encoding a fusion protein comprising an Ig chain and a polypeptide to induce tolerance. It is assumed that a polypeptide to which tolerance is desired encompasses any polypeptide. This assumption is based on the specification, because applicants used bacteriophage lambda c1 protein for tolerance, but it cannot be envisioned why tolerance would be desired against bacteriophage lambda c1 protein. Dal Porto (1993, PNAS, Vol. 90, pg 6671-6675) taught a cell line (J558L) comprising DNA encoding an H-2k^b-IgG heavy chain fusion protein. Vie (1992, PNAS, Vol. 89, pg 11337-11341) taught J558L transfected with DNA encoding an IL-2-IgM fusion protein. Arulanandam (1993, J. Exp. Med., Vol. 177, pg 1439-1450) taught lymphoid cell lines transfected with DNA encoding a CD2-IgM fusion protein (pg 1440, “Construction...” and pg 1441, “cells...”). Sekigawa taught a lymphoid cell line transfected with DNA encoding a CD4-IgG fusion protein (pg 5194, col. 1). Zwirner (1992, J. Immunol., Vol. 148, pg 272-276) taught a B-cell line transfected with DNA encoding an MHC-IgG fusion protein. Zambidis (1993) taught J558L transfected with DNA encoding a bacteriophage λ c1-IgG fusion protein. While the cells of Dal Porto, Vie, Arulanandam, Sekigawa, Zwirner and Zambidis were all tumor cells lines, their teachings correlate to the claimed invention because their fusion proteins are equivalent to the fusion proteins required in the claims. In addition, the tumor cells taught by Zambidis are the tumor cells disclosed on pg 36, line 16, of the instant application. Thus, the art

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at the time of filing taught cells encoding numerous fusion proteins that are equivalent to the fusion protein required in the claims. While Zambidis (1996, PNAS, Vol. 93, pg 5019-5024) taught the transfected tumor cells induced tolerance upon being introduced into an individual, Dal Porto, Vie, Arulanandam, Sekigawa and Zwirner taught the fusion protein induced an immune response and did not induce tolerance. Thus, the art at the time of filing did not teach how to induce tolerance using any DNA encoding an immunoglobulin fusion protein in a cell as required in the claims.

Adequate written description of a composition that induces tolerance requires more than a mere statement that it is part of the invention and reference to the method of making it. It is not sufficient to define a composition as being able to induce tolerance in a host or to define a protein as "containing at least one epitope to the antigen to which tolerance is desired". Disclosure of no more than that, as in the instant case, is simply a wish to know the identity of proteins that are capable of inducing tolerance when fused to an immunoglobulin molecule, and cells that are capable of inducing tolerance that express such fusion proteins. Naming a composition having a generic function in the absence of knowledge as any composition having such function is not a description of that material. Thus, claiming all compositions that induce tolerance without defining the structure of such compositions, or the requirements essential to obtain tolerance is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

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Applicants argue the skilled artisan would be able to make the composition claimed and administer the composition to a host. Applicants argument is off point because the rejection is based on the lack of description of compositions that induce tolerance as claimed.

Applicants provide the second declaration by Dr. Scott, paper number 35, which teaches making B-cells expressing a fusion protein comprising IgG and full length MBP, full length GAD65, insulin B chain-9-23, IRBP-161-180, full length bacteriophage λ c1 protein, or full-length ovalbumin. The antigens used in the fusion protein were not described in the specification as originally filed. Therefore, the declaration does not correlate to the disclosure as originally filed.

The declaration states mice were injected with B-cells expressing MBP-IgG followed by passive transfer of MBP-specific T-cell (para. 4, line 8). While the specification contemplates using "tolerogenic epitopes" of MBP to obtain tolerance to MBP (pg 20, lines 3-18, taken as a whole which discusses epitopes used in the fusion proteins; see especially "If the epitope is one that stimulates an immunodominant response, tolerance to that epitope can also result in tolerance to an antigen containing the epitope. Specific examples include... ..myelin basic protein..."), the specification does not contemplate using full length MBP in the fusion protein. It is noted that the mice still had EAE. As such the declaration does not correlate to the specification as originally filed.

The declaration states NOD mice were injected with NOD B-cells expressing GAD-IgG or B9-23-IgG fusion protein (para. 5). A lower percentage of mice exhibited signs of diabetes as

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compared to mice injected with B-cells expressing lambda λ c1-IgG. GAD was not described in the specification as originally filed. Insulin B chain - residues 9-23 was not described in the specification as originally filed. It is noted that the mice still had inflammation (para. 4, 5 lines from the bottom). Therefore, the example does not correlate to the disclosure as originally filed.

The declaration states "autoimmune uveitis" mice were injected with B-cells expressing IRBP-161-180-IgG followed by challenge with IRBP. The results are summarized in Agarwal (2000, J. Clin. Investig., Vol. 106, pg 245-252). The example does not correlate to the disclosure as originally filed because the use of an IgG hypervariable region in the fusion protein was not contemplated in the specification as originally filed (see Agarwal, pg 5020, col. 2, last full para.; pg 5019, col. 2, 2nd para., 1st sentence). The specification contemplated using the entire variable region of IgG (pg 32, line 15). The hypervariable region is a portion (15-20%) of the variable region (Kuby, 1994, Immunology, 2nd ed., WH Freeman and Company, pg 117, col. 1, first full para., lines 1-6; pg 135, col. 1, second sentence). Therefore, use of the entire variable region does not support use of the hypervariable region. While Silver (1995) taught the IRBP-161-180 residue, use of IRBP, specifically residue 161-180, was not contemplated in the specification as originally filed. In fact, the IRBP-161-180 residue was not available at the time of filing (effective filing date=2-11-1994).

The declaration states mice were injected with non-tumor lymphoid cells expressing full length bacteriophage λ c1-IgG (para. 7). The results are summarized in Kang (PNAS, 1999, Vol. 96, pg 8609-8614). The example does not correlate to the disclosure as originally filed because

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inserting the antigen into an IgG1 heavy chain between the 5' FR1 and FR1 repeat was not contemplated in the specification as originally filed (see reasoning in the para. above and Kang, pg 8610, col 1, "Retroviral construct...", 2nd para., second sentence). Nor was the 320-bp DNA fragment encoding p1-102 contemplated in the specification as originally filed (pg 8610, col. 1, line 10). Furthermore, Kang clearly states that in 1999, it was unknown whether full-length protein would be processed, presented and tolerized in the same manner as selected epitopes. Therefore, the example does not correlate the disclosure as originally filed.

Full length ovalbumin does not have a disclosed use for inducing tolerance. The specification does not contemplate using full length ovalbumin. Therefore, para. 8 does not correlate to the disclosure as originally filed.

Overall, the non-tumor lymphoid cells comprising a retroviral vector encoding a bacteriophage λ c1-IgG fusion protein (Example V) do not correlate to the claimed invention because bacteriophage λ c1 is not an "antigen to which tolerance is desired," the specification and the art at the time of filing do not teach any other fusion proteins that induce tolerance, and the specification does not provide adequate correlation between the structure or function of bacteriophage λ c1 12-26 peptide and any other peptide such that tolerance could be induce. Therefore, the specification does not provide adequate written description for a cell that induces tolerance as claimed.

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3. Claims 69-78 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a non-tumor, lymphoid cell comprising DNA encoding a fusion protein operably linked to a promoter, wherein said fusion protein comprises bacteriophage λ c1 peptide 12-26 and an IgG heavy chain, does not reasonably provide enablement for a non-tumor, lymphoid cell comprising DNA encoding a fusion protein comprising i) an immunoglobulin heavy or light chain and ii) a protein having an epitope of the antigen to which tolerance is desired. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

Claim 69 is directed toward a composition for inducing tolerance to an antigen comprising a non-tumor lymphoid cell transfected with a vector encoding a fusion protein comprising i) an immunoglobulin heavy or light chain and ii) a protein having an epitope of the antigen to which tolerance is desired, wherein said composition induces tolerance to the antigen. The specification does not enable any fusion protein as broadly required in the claim to induce tolerance in a host. Since the pharmaceutical composition claimed requires cell having DNA encoding such a fusion protein, the specification does not enable any non-tumor lymphoid cell that induces tolerance in a host as claimed.

The specification does not enable using a cell comprising DNA encoding any fusion protein comprising an Ig chain and a polypeptide to induce tolerance as claimed. It is assumed that a polypeptide to which tolerance is desired encompasses any polypeptide. This assumption

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is based on the specification, because applicants used bacteriophage lambda c1 protein for tolerance, but it cannot be envisioned why tolerance would be desired against bacteriophage lambda c1 protein. Dal Porto (1993, PNAS, Vol. 90, pg 6671-6675) taught a cell line (J558L) comprising DNA encoding an H-2k^b-IgG heavy chain fusion protein. Vie (1992, PNAS, Vol. 89, pg 11337-11341) taught J558L transfected with DNA encoding an IL-2-IgM fusion protein. Arulanandam (1993, J. Exp. Med., Vol. 177, pg 1439-1450) taught lymphoid cell lines transfected with DNA encoding a CD2-IgM fusion protein (pg 1440, "Construction..." and pg 1441, "cells..."). Sekigawa taught a lymphoid cell line transfected with DNA encoding a CD4-IgG fusion protein (pg 5194, col. 1). Zwirner (1992, J. Immunol., Vol. 148, pg 272-276) taught a B-cell line transfected with DNA encoding an MHC-IgG fusion protein. Zambidis (1993) taught J558L transfected with DNA encoding a bacteriophage λ c1-IgG fusion protein. Thus, the art at the time of filing taught cells encoding numerous fusion proteins that are equivalent to the fusion protein required in the claims. While the cells of Dal Porto, Vie, Arulanandam, Sekigawa, Zwirner and Zambidis were all tumor cells lines, their teachings correlate to the claimed invention because their fusion proteins are equivalent to the fusion proteins required in the claims. In addition, the tumor cells taught by Zambidis are the tumor cells disclosed on pg 36, line 16, of the instant application. While Zambidis (1996, PNAS, Vol. 93, pg 5019-5024) taught the transfected tumor cells induced tolerance upon being introduced into an individual, Dal Porto, Vie, Arulanandam, Sekigawa and Zwirner taught the fusion protein induced an immune response and did not induce tolerance. Thus, the art at the time of filing did not teach how to

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induce tolerance using any DNA encoding an immunoglobulin fusion protein in a cell as required in the claims.

The specification teaches transfecting non-tumor bone marrow cells with a retroviral vector encoding the bacteriophage λ c1-IgG fusion protein (pg 42, Example 5). Since the time of filing, Zambidis (1997, Molecular Med., Vol. 3, pg 2174-82) taught administering the retrovirally transduced bone marrow cells to mice, injecting the mice later with the bacteriophage λ c1 peptide or a control antigen, testing the antibody and CTL response of the mice, and comparing the response of test mice to controls wherein a decreased antibody or CTL response in the test mice as compared to controls indicated tolerance was induced against bacteriophage lambda c1 (pg 213, col. 2, last 4 lines; pg 214, col. 2, "Tolerance..."). However, neither the specification or Zambidis provide a reason why one of skill would want to induce tolerance against the lambda c1 protein. Therefore, the 12-26 peptide is not an "antigen to which tolerance is desired" as claimed.

Applicants arguments regarding the second declaration have been addressed above in the written description rejection. Applicants arguments regarding the first declaration have been reiterated and have been addressed in the previous office action. The declarations are not persuasive because they require fusion proteins that were not contemplated in the specification as originally filed.

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The rejection of claims 52-68 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been withdrawn because the claims have been canceled.

4. Claims 69-78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

The metes and bounds of the polypeptides encompassed by “a polypeptide containing at least one epitope of the antigen to which tolerance is desired to be induced” (claim 69) cannot be envisioned. The structure or function of the polypeptides cannot be envisioned. It is unclear what antigens are desired. The structure of antigens that are tolerogenic is not defined in the specification or the art at the time of filing. The requirements to induce tolerance against an antigen are not defined in the specification or the art at the time of filing. The specification states the antigens for use in inducing tolerance are capable of inducing an antibody response in the individual (pg 11, line 26), yet applicants argue an antigen that induces an antibody response is not a “desired antigen” because it is not within the metes and bounds of the claim (see response to 102 rejection over Zanetti). For example, the bacteriophage lambda c1 protein is used by applicants, but it cannot be envisioned why one would want to induce tolerance against bacteriophage lambda c1 protein. Furthermore, “containing” is closed language, and the specification does not teach a polypeptide “containing” only such an epitope.

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Claim 70 is indefinite because nucleic acid sequences do not comprise vectors. Vectors comprise nucleic acid sequences.

Claim 71 is indefinite because there should be a comma after “retroviral vector” to comply with standard Markush Group format.

Claim 72 is indefinite because it is unclear if any of the “two or more copies of the nucleic acid sequence” are the “nucleic acid sequence” in claim 69, or if the “two or more copies of the nucleic acid sequence” are in addition to the “nucleic acid sequence” in claim 69.

Applicants argue the phrase is similar to the suggested phrase. Applicants argument is not persuasive because the phrase contains “copies” which was not in the suggested phrase.

Claim 74 is indefinite because the phrase “polypeptide or portion thereof” lacks antecedent basis in claim 69. “Or portion thereof” was deleted in the parent claim and should be deleted in claim 74.

Claim Rejections - 35 USC § 102

The rejection of claims 52-55, 58 and 65-68 under 35 U.S.C. 102(e) as being anticipated by Zanetti (US Patent 5,508,386, April 16, 1996) has been withdrawn because the claims have been canceled.

The rejection of claims 52-55 under 35 U.S.C. 102(e) as being anticipated by Romet-Lemonne (US Patent 6,258,358, July 10, 2001) as supported by Romet-Lemonne (US Patent 6,248,332, June 19, 2001) has been withdrawn because the claims have been canceled.

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The rejection of claims 52-55, 58, 59, 61 and 65-68 under 35 U.S.C. 102(b) as being anticipated by Zambidis (Feb. 1, 1993, J. Cellular Biochem., Vol. 9, No. 17, Part B, page 251) has been withdrawn because the claims have been canceled.

5. New claim 69 is rejected under 35 U.S.C. 102(e) as being anticipated by Zanetti of record (US Patent 5,508,386, April 16, 1996).

Zanetti taught a J588 bone marrow tumor cell line comprising a vector encoding a fusion protein comprising an IgG heavy chain and an epitope of the plasmodium falciparum circumsporozoite protein. The cells were in DMEM which is a "pharmacologically acceptable excipient" (col. 5, line 64, through col. 7, line 17). The J588 bone marrow tumor cell is a "hematopoietic cell" as claimed because J588 is "hematopoietic," because "hematopoietic cells" are isolated from the bone marrow. The term "non-tumor" does not apply to "hematopoietic cell" (see 112/2nd). The plasmodium fusion protein induced an antibody response against the plasmodium antigen (col. 10, line 49) which is equivalent to inducing tolerance as claimed. Overall, the structure of the cell taught by Zanetti is equivalent to the cell claimed and inherently induces tolerance as claimed. Since the specification teaches a bacteriophage λ cI epitope-IgG fusion protein is part of the invention, there is no reason to believe that a plasmodium-IgG fusion protein is excluded from the claim. The specification and the art at the time of filing does not teach the requirements to obtain tolerance, the antibody response that occurs in a host following administering a fusion protein of the invention (but before challenging with the antigen), or that inducing tolerance excludes inducing an antibody response as taught by Zanetti. In fact, the

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specification teaches antigens used in the fusion protein induce an antibody response (pg 11, line 26 and pg 11, line 26). Therefore, obtaining tolerance to an antigen using a cell expressing the antigen in an IgG fusion protein encompasses inducing an antibody response against the antigen. As such, inducing an antibody response as taught by Zanetti anticipates “induces tolerance” as claimed. Since the patent office does not have the means to determine the ability of the composition of Zanetti to induce tolerance, given the reasoning above, the composition of Zanetti inherently induces tolerance.

Applicants arguments regarding Zanetti have been considered to the extent that they relate to the rejection of new claim 69, and are addressed in the preceding paragraph.

6. Claims 69 is rejected under 35 U.S.C. 102(b) as being anticipated by Zambidis of record (Feb. 1, 1993, J. Cellular Biochem., Vol. 9, No. 17, Part B, page 251).

Zambidis taught a J588 bone marrow tumor cell line comprising a vector encoding a fusion protein comprising an IgG heavy chain and a bacteriophage λ cl protein on the N-terminus. The J588 bone marrow tumor cell is a “hematopoietic cell” as claimed because J588 is “hematopoietic,” because “hematopoietic cells” are isolated from the bone marrow. The term “non-tumor” applies to “lymphoid” and does not apply to “hematopoietic cell” (see 112/2nd).

The J588 cell line was inherently in culture medium, which is a “pharmaceutically acceptable excipient” as claimed. Recombinant molecules were purified from the cells. Survival of the cells is essential to obtain recombinant molecules. Culture medium is essential to obtain survival of the cells. Therefore, culture medium is essential to purify recombinant molecules

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from the cells. Since culture medium is essential to purify recombinant molecules from J588, J588 inherently were in culture medium.

The fusion protein of Zambidis is the fusion protein described in Examples I-V in the instant disclosure. The structure of the cell taught by Zambidis is equivalent to the cell claimed. Therefore, the cell of Zambidis inherently “induces tolerance to the antigen in an individual.”

Applicants argue Zambidis did not teach inducing tolerance (pg 31 of response). Applicants argument is not persuasive. The phrase “wherein said composition induces tolerance to the antigen in an individual” is a functional limitation of the product claimed. Therefore, the claim does not require inducing tolerance; the claim merely requires the product is capable of inducing tolerance. The cell of Zambidis meets the limitation because the cells are capable of inducing tolerance.

Applicants argue Zambidis did not teach the pharmaceutically acceptable excipient. Applicants argument is not persuasive for reasons cited above.

Claim Rejections - 35 USC § 103

The rejection of claims 52-55, 58 and 62-68 under 35 U.S.C. 103(a) as being unpatentable over Zanetti in view of GenBank Record Numbers has been withdrawn because the claims have been canceled.

The rejection of claims 52, 55-59, 61 and 65-68 under 35 U.S.C. 103(a) as being unpatentable over Zambidis (Feb. 1, 1993, J. Cellular Biochem., Vol. 9, No. 17, Part B, page

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251) in view of Zanetti (Jan. 30, 1992, Nature, Vol. 355, pg 476-477) and Chambers (Feb. 1992, PNAS, USA, Vol. 89, pages 1026-1030) has been withdrawn because the claims have been canceled.

7. Claims 69-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chambers (Feb. 1992, PNAS, USA, Vol. 89, pages 1026-1030) in view of Zambidis (Feb. 1, 1993, J. Cellular Biochem., Vol. 9, No. 17, Part B, page 251).

This rejection was not previously required because the combination of elements in the claims was not previously required.

Chambers taught PBL transfected with a retroviral vector encoding a protein (IL-6) (pg 1026, col. 2, "Retroviral vector construct..." and "PBL infection..."). Chambers did not teach the retrovirus encoded a fusion protein comprising an immunoglobulin and an antigen as required in claim 69.

However, Zambidis taught a cell line transfected with a vector encoding a fusion protein comprising an IgG heavy chain and a bacteriophage λ cl protein on the N-terminus.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make PBL comprising a retroviral vector encoding a protein as taught by Chambers wherein the protein was a fusion protein comprising an IgG heavy chain and a bacteriophage λ cl protein on the N-terminus as taught by Zambidis. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the IL-6 with the fusion protein to perform *in vivo* and *in vitro* tolerance experiments with this fusion protein as

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suggested by Zambidis (last sentence). One of ordinary skill in the art at the time the invention was made would have been motivated to replace the tumor cell line of Zambidis with the non-tumor PBL as taught by Chambers to prevent causing tumors in *in vivo* tolerance experiments as suggested by Zambidis. One of ordinary skill in the art at the time the invention was made would have been motivated to use a retroviral vector as taught by Chambers in the cell of Zambidis because retroviral vectors were the most efficient means of introducing genes into a variety of tissues, particularly cells of the hematopoietic system as taught by Chambers (pg 1026, col. 1, para. 2, second sentence).

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR

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1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

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MICHAEL C. WILSON
PATENT EXAMINER